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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/494,332	01/28/00	GORMAN	K

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EXAMINER	
GOLDBERG, J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/494,332	Applicant(s) GORMAN ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 46* is/are allowed.

6)☒ Claim(s) *1-24,26-31,33,35,37,39,41 and 43-45* is/are rejected.

7)☒ Claim(s) *32,34,36,38,40 and 42* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed March 27, 2000. Currently, claims 1-46 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Specification

4. It is noted that SEQ ID NO: 10 and 1 are 100% identical. Furthermore, SEQ ID NO: 11 consists of 24 of the 25 nucleotides of SEQ ID NO: 2.

The response has amended the sequence listing to reflect the correct SEQ ID NO: 11 as presented in the claims such that SEQ ID NO: 11 is identical to SEQ ID NO: 2.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9, 16-24, 26-30, 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 9, 24 are directed to "co-detecting" such that the "co-detecting" is simultaneous, however, as amended, Claim 1 is no longer drawn to co-detecting. Claim 1 is a method of detecting either HCV or HIV. Similarly, Claim 16 is no longer co-detecting.

B) Claims 16-24, 45 are indefinite because it is unclear exactly is required of step (a). Step (a) recites "...to produce reverse transcription of DNA from HIV RNA to produce reverse transcription products comprising (a)... and (b), (c) or (d)...". It is unclear why there is an "and" prior to (b). It is unclear whether this "and" requires that (a) must be present or whether this is merely a typographical error. Furthermore, in Step (b) the claim recites a list, however prior to step (b) the comma appears to be missing such that it is clear that a, b, c, or d is applicable.

C) Claim 26-30 are rejected as indefinite because Claim 10 makes no references to detection of IPC-specific amplification products. It is unclear whether the claim was intended to depend upon Claim 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991).

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4).

Han does not specifically teach amplifying or detecting HCV using the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the

> claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have chosen SEQ ID NO: 1 and 2, which flank ORF3. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose.

Response to Arguments

Based upon the amendment to the claims, the claim no longer require the detection of both HIV and HCV, therefore, Han obviates the claims alone.

The response traverses the rejection. The response asserts that Han reference does not provide oligonucleotide sequences for any particular probe or primer for this 5' UTR, let alone the particular oligonucleotide sequences of the instant invention. This argument appears directed to a reason why Han is not a 102 reference. This argument has been reviewed but is not convincing because Han has taught four primers which amplify 5' UTR and two probes for this region. Han teaches Primer 51 was used to prime cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a.

The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides the teaching "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers.

Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 1, 3-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backus et al (US Pat 6,001,558, December 1999).

Backus et al. (herein referred to as Backus) teaches amplification and detection of HIV-1 and HIV-2. Backus teaches oligonucleotides which amplify HIV-1 nucleic acids including oligonucleotides which are SEQ ID NO: 3 and 5. Backus also teaches an oligonucleotide which comprises the nucleotides of SEQ ID NO: 4. Backus, furthermore, teaches oligonucleotides which amplify HIV-2 nucleic acids including oligonucleotides which are SEQ ID NO: 6 and 7. Backus also teaches oligonucleotide probes of SEQ ID NO: 13, 14 and 16 for HIV-1 and HIV-2. The primers choosen were from identified highly conserved sequence regions (col. 10, lines 50-60). Backus teaches that a biological sample is used which included cellular-or viarl material, hair, body fluids, or cellular material containing nucleic acids which may be detected (limitations of Claims 8 and 23).

Backus does not specifically teach amplifying or detecting HIV using the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed HIV-1/2 sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Backus to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the HIV-1 and HIV-2 as taught by Backus. The ordinary artisan would have used the probes and primers from Backus, based upon the detailed analysis provided that these probes and primers were for conserved regions among the numerous isolates. The ordinary artisan would have combined the teachings of Backus for the express benefit of diagnosing more than one viral agent in samples of infected individuals.

Response to Arguments

Based upon the amendment to the claims, the claim no longer require the detection of both HIV and HCV, therefore, Backus obviates the claims alone.

The response traverses the rejection. The response asserts that the Backus reference does not provide oligonucleotide sequences for any particular probe or primer for this HIV 1/ 2 sequence, let alone the particular oligonucleotide sequences of the instant invention. This argument appears directed to a reason why Backus is not a 102 reference.

The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides the teaching "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maertens et al (US Pat. 5,846,704, December 1998).

Maertens et al (US Pat. 5,846,704, December 8, 1998) teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55). Maertens provides specific primers for each of the isolates and universal primers which may be used (Table 4 and 5).

SEQ ID NO: 1 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 17-25 of the instant application are identical to nucleotides 1-9 of Maertens.

SEQ ID NO: 2 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 5-25 of the instant application are identical to nucleotides 1-20 of Maertens.

Maertens does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural and functional homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method and primers of Maertens to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Maertens. The instant primers overlap the primers of Maertens such that it would be presumed that these primers would have the same properties and amplify the same regions. Moreover, any primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

9. Claims 1-15 and newly added Claims 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) or Maertens et al (US Pat. 5,846,704, December 1998).and Backus et al (US Pat 6,001,558, December 1999) in view of Nedjar et al (J. of Virological Methods, Vol. 35, No. 3, pg 297-304).

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4).

Maertens et al (US Pat. 5,846,704, December 8, 1998) teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of

HCV (abstract). Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55). Maertens provides specific primers for each of the isolates and universal primers which may be used (Table 4 and 5). SEQ ID NO: 1 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 17-25 of the instant application are identical to nucleotides 1-9 of Maertens. SEQ ID NO: 2 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 5-25 of the instant application are identical to nucleotides 1-20 of Maertens.

Backus et al. (herein referred to as Backus) teaches amplification and detection of HIV-1 and HIV-2. Backus teaches oligonucleotides which amplify HIV-1 nucleic acids including oligonucleotides which are SEQ ID NO: 3 and 5. Backus also teaches an oligonucleotide which comprises the nucleotides of SEQ ID NO: 4. Backus, furthermore, teaches oligonucleotides which amplify HIV-2 nucleic acids including oligonucleotides which are SEQ ID NO: 6 and 7. Backus also teaches oligonucleotide probes of SEQ ID NO: 13, 14 and 16 for HIV-1 and HIV-2. The primers chosen were

from identified highly conserved sequence regions (col. 10, lines 50-60). Backus teaches that a biological sample is used which included cellular-or viral material, hair, body fluids, or cellular material containing nucleic acids which may be detected (limitations of Claims 8 and 23).

Han and Backus do not specifically teach co-amplifying or co-detecting HCV and HIV using the primers of the instant claimed invention.

However Nedjar teaches a method of co-amplification of specific sequences of HCV and HIV by using PCR assays. Nedjar teaches that primer pairs from HCV and HIV-1 sequences were used (pg 299). Nedjar teaches the conditions of the multiplex reaction. Nedjar teaches the ability to co-amplify specific sequence from two different viral genomes in the same reaction mixture offers the possibility of simultaneous detection and diagnosis of more than one viral agent in serum samples of infected individuals.

Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 5' UTR HCV and the HIV-1/2 sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han and Backus in view of Nedjar to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han and primers from HIV-1 and HIV-2 as taught by Backus. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have chosen SEQ ID NO: 1 and 2, which flank ORF3. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose. The ordinary artisan would have used the probes and primers from Backus, based upon the detailed analysis provided that these probes and primers were for conserved regions among the numerous isolates. The ordinary artisan would

have combined the teachings of Han and Backus in view of Nedjar for the express benefit of diagnosing more than one viral agent in samples of infected individuals. The ordinary artisan would have recognized that the detection of more than one viral agent would have been ideal for saving time, and reagents. The multiplexing of numerous primers into a single reaction has the express benefit of saving reagent by limiting the number of assays and also saving time of scientists since the results may be obtained simultaneously. Thus, the ordinary artisan would have combined the teachings of detecting HCV with the teachings of detecting HIV-1 and HIV-2.

Response to Arguments

The response traverses the rejection.

The response asserts that Han reference does not provide oligonucleotide sequences for any particular probe or primer for this 5' UTR nor the HIV 1/ 2 region, let alone the particular oligonucleotide sequences of the instant invention. This argument appears directed to a reason why Han is not a 102 reference.

The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides the teaching

"to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the primer selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

The response asserts that Multiplex PCR is unpredictable at best. This argument has been reviewed but is not convincing because multiplexing using multiple primers was routine in the art at the time the invention was made. While the reference, Elnifro, teaches that optimization of multiplex PCRs can pose several difficulties...."(pg 559, col. 2), the reference also provides solutions to many of these "difficulties". For example, Elnifro teaches "the optimization of multiplex PCR should aim to minimize or reduce non-specific interactions". Moreover, Elnifro teaches primer design is critical (pg 560, col. 1). Additionally, in response to the assertion that multiplex PCR optimization is unpredictable, however, Kimpton teaches numerous parameters to optimize in multiplex PCR. Kimpton was provided much before the time of the filing to illustrate that

optimization of multiplex reactions was routine. Specifically Kimpton teaches optimizing buffer concentration, primer concentration, deoxynucleotide triphosphate concentration, Taq polymerase concentration, template DNA concentration, number of amplfication cycles, denaturing temperature, annealing temperature, non-specific amplfication products, ionic strenth and pH, and gel types. The teachings of Kimpton teach the ordinary artisan how to optimize the conditions of Nedjar to obtain optimal results. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the multiplex selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Claims 31, 33, 35, 37, 39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) or Maertens et al (US Pat. 5,846,704, December 1998).and/or Backus et al (US Pat 6,001,558, December 1999) in view of Nedjar et al (J. of Virological Methods, Vol 35, No. 3, pg 297-304) as applied to Claim 1, 3-13, 40-44 above, and further in view of Ahern

(www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Neither Han, Maertens, Backus nor Nedjar specifically teaches packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Han, Maertens and Backus in view of Nedjar with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Han, Maertens and Backus into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Han's, Maertens', Backus', or Nedjar's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers, taught by Han or Maertens and/or Backus in view of Nedjar into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-64 of copending Application No. 09/493,353. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to a method of detecting HCV 5' UTR using SEQ ID NO: 1 and 2 of the instant application which are identical to SEQ ID NO: 2 and 7 of 09/493,353.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

12. The instant IPC region and primers to the synthetic region are novel over the prior art. The SEQ ID NO: 8, 9 and 15 are not previously known in the art. However, Picone et al. (US Pat. 5,491,225, February 1996) and Blasczyk et al (Beitrage Zur Infusionstherapie Und Transfusionmedizin, Vol 34, pg 236-241, 1997-abstract only) teach incorporating IPC RNA into an assay. Picone et al. (herein referred to as Picone) teaches "internal positive control oligonucleotide sequences" are a recombinant or synthetic oligonucleotides that ensure assay users that the amplification process has occurred in the event that the sample being tested has no target nucleic acid. Additionally, Blasczyk et al. (herein referred to as Blascyzk) teaches a pair of primers which amplify a fragment of the human growth hormone gene was included as an internal positive amplification control. The presence or absence of specific PCR amplification allowed definite allele assignment without the need for any postamplification specificity step. Additionally, Blasczyk teaches that the internal positive control primers indicate a successful PCR amplification (abstract).

Thus, while the concept of internal control regions and primers to amplify are known in the art, the specific sequences of the instant used primers are novel.

Conclusion

13. **Claims 25, 46 are allowable over the prior art.** Claims **32, 34, 36, 38, 40, 42, are** objected to as being dependent upon a rejected base claim, but would be allowable

if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Claims 1-24, 26-31, 33, 35, 37, 39, 41, 43-45 are not allowable.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Research Genetics, Designer PCR, Nucleic Acids Research, Vol. 22, No. 15, August 11, 1994 provides an advertisement for a product specifically designed to select primers given a set of parameters.

B) Kimpton et al. "Evaluation of an automated DNA profiling system employing multiplex amplification of four terameric STR loci" Int. J. Leg. Med. Vol. 106, pg. 302-311, 1994. Kimpton teaches optimization conditions for multiplex PCR.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
April 24, 2001 JEG

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600